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- Declaration under Rule 4.17:**
— *of inventorship (Rule 4.17(iv)) for US only*
- Published:**
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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
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(54) Title: CYANOMETHYL DERIVATIVES AS CYSTEINE PROTEASE INHIBITORS

(57) Abstract: The present invention is directed to cyanomethyl derivatives that are inhibitors of cysteine protease, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

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INTERNATIONAL SEARCH REPORT

National Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/062 A61K38/05 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/24460 A (NOVARTIS ERFIND VERWALT GMBH ;ALTMANN EVA (CH); LATTMANN RENE (CH)) 20 May 1999 (1999-05-20) page 1, lines 1-3; page 6, lines 4-9; page 31, compound 13; page 43, compound 49; page 58, compound 110; page 61, compound 130; claims 1,2 ---	1-37
X	WO 00/55126 A (BRYANT CLIFFORD M ;VENKATRAMAN SHANKAR (US); AXYS PHARM INC (US);) 21 September 2000 (2000-09-21) page 26, line 27 -page 27, line 12; claim 1 --- -/--	1-37

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *&* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/37979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/58886 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); MISSBACH MARTIN (C) 16 August 2001 (2001-08-16) page 1, line 1-4 page 1, line 17 -page 2, line 8; claim 1 ---	1-37
X	WO 00/49008 A (EDWARDS PHILIP NEIL ;LARGE MICHAEL STEWART (GB); OLDFIELD JOHN (GB) 24 August 2000 (2000-08-24) page 1, line 1-6; claim 1 ---	1-37
X	WO 01/19816 A (BOEHRINGER INGELHEIM PHARMA ;EMMANUEL MICHEL J (US); FRYE LEAH L () 22 March 2001 (2001-03-22) page 1, line 11-15 page 6, line 25 -page 11, line 8; claim 1 ---	1-37
X	WO 00/51998 A (BOEHRINGER INGELHEIM PHARMA) 8 September 2000 (2000-09-08) page 1, line 9-13 page 78, line 19 -page 81, line 9; claims 21,31 -----	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/37979

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 34-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9924460	A	20-05-1999	AU 751669 B2 22-08-2002
			AU 1487399 A 31-05-1999
			BR 9813197 A 29-08-2000
			CA 2306313 A1 20-05-1999
			CN 1278244 T 27-12-2000
			WO 9924460 A2 20-05-1999
			EP 1028942 A2 23-08-2000
			HU 0004400 A2 29-04-2002
			ID 24931 A 31-08-2000
			JP 2001522862 T 20-11-2001
			NO 20002320 A 04-07-2000
			NZ 503889 A 26-07-2002
			PL 340819 A1 26-02-2001
			SK 6572000 A3 09-10-2000
			TR 200001189 T2 21-09-2000
			US 2004029814 A1 12-02-2004
			US 6353017 B1 05-03-2002
			ZA 9810073 A 05-05-1999
			TW 527362 B 11-04-2003
WO 0055126	A	21-09-2000	AT 259782 T 15-03-2004
			AU 3746100 A 04-10-2000
			AU 769736 B2 05-02-2004
			AU 3748600 A 04-10-2000
			BG 106003 A 28-06-2002
			BG 106013 A 31-05-2002
			BR 0009042 A 26-12-2001
			BR 0009043 A 08-01-2002
			CA 2368122 A1 21-09-2000
			CA 2368148 A1 21-09-2000
			CN 1362947 T 07-08-2002
			CN 1364155 T 14-08-2002
			CZ 20013217 A3 17-04-2002
			CZ 20013248 A3 17-04-2002
			DE 60008369 D1 25-03-2004
			EE 200100485 A 17-02-2003
			EE 200100487 A 17-02-2003
			EP 1178958 A2 13-02-2002
			EP 1161415 A2 12-12-2001
			HR 20010737 A1 31-10-2002
			HR 20010738 A1 31-12-2002
			HU 0200347 A2 29-06-2002
			HU 0200503 A2 29-06-2002
			JP 2002539191 T 19-11-2002
			JP 2002539192 T 19-11-2002
			NO 20014484 A 26-10-2001
			NO 20014485 A 05-11-2001
			NZ 514234 A 27-02-2004
			PL 350453 A1 16-12-2002
			PL 350456 A1 16-12-2002
			SK 12882001 A3 04-04-2002
			SK 12892001 A3 04-06-2002
			TR 200103337 T2 21-03-2002
			TR 200103390 T2 21-05-2002
			TR 200201874 T2 21-10-2002
			WO 0055125 A2 21-09-2000
			WO 0055126 A2 21-09-2000
			US 2002086996 A1 04-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0055126 A		US 2003096796 A1	22-05-2003
		US 2003119788 A1	26-06-2003
		US 6455502 B1	24-09-2002
		US 6476026 B1	05-11-2002
		ZA 200107494 A	11-09-2002
		ZA 200107495 A	11-09-2002
WO 0158886 A	16-08-2001	AU 764334 B2	14-08-2003
		AU 4642601 A	20-08-2001
		BR 0108118 A	25-02-2003
		CA 2396158 A1	16-08-2001
		CN 1398260 T	19-02-2003
		CZ 20022721 A3	13-11-2002
		WO 0158886 A1	16-08-2001
		EP 1254124 A1	06-11-2002
		HU 0300148 A2	28-05-2003
		JP 2003522764 T	29-07-2003
		NO 20023780 A	09-08-2002
		NZ 519940 A	27-02-2004
		SK 11462002 A3	09-01-2003
		TR 200201752 T2	21-10-2002
		US 2003203919 A1	30-10-2003
		US 2001016207 A1	23-08-2001
		ZA 200206218 A	05-08-2003
WO 0049008 A	24-08-2000	AU 2560000 A	04-09-2000
		EP 1155011 A1	21-11-2001
		WO 0049008 A1	24-08-2000
		JP 2002537294 T	05-11-2002
WO 0119816 A	22-03-2001	AT 244235 T	15-07-2003
		AU 7081800 A	17-04-2001
		BG 106483 A	31-10-2002
		CA 2385130 A1	22-03-2001
		CN 1384830 T	11-12-2002
		CZ 20020844 A3	12-06-2002
		DE 60003702 D1	07-08-2003
		DE 60003702 T2	22-04-2004
		DK 1218372 T3	20-10-2003
		EE 200200132 A	15-12-2003
		EP 1218372 A1	03-07-2002
		ES 2199856 T3	01-03-2004
		HU 0302380 A2	01-03-2004
		JP 2003529546 T	07-10-2003
		NO 20021207 A	12-03-2002
		PT 1218372 T	28-11-2003
		SI 1218372 T1	31-12-2003
		SK 4902002 A3	10-09-2002
		US 2002058809 A1	16-05-2002
		WO 0119816 A1	22-03-2001
WO 0051998 A	08-09-2000	US 2003225271 A1	04-12-2003
		US 2003225270 A1	04-12-2003
		US 6420364 B1	16-07-2002
		CA 2360740 A1	08-09-2000
		EP 1159273 A1	05-12-2001
		JP 2002538151 A	12-11-2002
		US 6608057 B2	19-08-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0051998	A	US 2002091259 A1	11-07-2002
		WO 0051998 A1	08-09-2000
		US 2003158406 A1	21-08-2003
		US 6395897 B1	28-05-2002
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